ORGANIC CHEMISTRY







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Cite this: *Org. Chem. Front.*, 2020, **7**, 2082

Dual N-heterocyclic carbene/photocatalysis: a new strategy for radical processes

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Received 8th May 2020, Accepted 23rd June 2020 DOI: 10.1039/d0qo00494d

rsc.li/frontiers-organic

While N-heterocyclic carbenes (NHCs) have played an important role as Lewis-base organocatalysts and developed recently into a full chapter of this exciting area of organocatalysis, NHC-catalyzed single-electron-transfer (SET) processes are still challenging and underdeveloped. Recently, NHC catalysis has been successfully combined with photoredox catalysis for SET reactions and this turned out to be a promising strategy. This article focuses on the recent advances of the combination of photoredox catalysis with NHC catalysis.

In the past decades, N-heterocyclic carbenes (NHCs) have witnessed remarkable achievements, and they are complementary to other organocatalysts and enable the creation of new activation modes that were previously unobtainable. A driving force is the great variety of reactive intermediates that can be generated with NHCs (Scheme 1A). Despite this progress, most of these transformations proceed *via* electron-pair-transfer pathways; the corresponding reactions *via* single-electron-transfer (SET) processes remain challenging.²

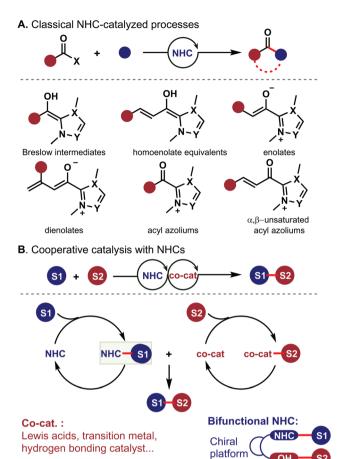
In recent years, cooperative catalysis with NHCs has remarkably improved the reaction efficiency and selectivity that are unobtainable by using single-catalyst systems (Scheme 1B). Interestingly, cooperative NHC/Lewis acid catalysis has strongly dominated this field,4 with comparatively less synergistic combination of NHC catalysis with other types of catalysis reported in the literature.3-5 Recently, there has been growing interest in harnessing the synergistic interplay of NHCs and photochemistry to develop new activation modes that provide more efficient and selective alternatives to classical approaches. An early example of dual NHC/photocatalysis was reported by Rovis and co-workers.6 In their system, the photocatalyst Ru (bpy)₃Cl₂ and NHC were employed for the α-acylation of tertiary amines. In 2016, an NHC/photo co-catalyzed γ-dichloromethylenation of enal was reported by Sun and coworkers.^{2g} Although these examples have shown the synthetic utility of dual NHC/photocatalysis, further development of this strategy to create new activation modes is still highly desirable. This manuscript aims to provide a brief summary of lightdriven NHC-catalyzed reactions and highlight recent publications in this area.

At present, there are two types of reaction modes associated with dual NHC/photocatalysis. One is the combination of classical NHC-intermediates and the generated radicals *via* photocatalysis. The other is the use of a new kind of NHC-derived radical intermediate *via* photocatalysis (Scheme 1C).

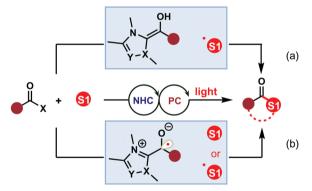
Recently, Ye and co-workers have made important contributions to dual NHC/photocatalysis by using reaction mode a. They successfully realized the γ - and ϵ -alkylation of enals via dual NHC/photocatalysis, offering direct access to γ- and εalkylated esters 3 in very good yields. Notably, the challenging vicinal all-carbon quaternary centers could be efficiently constructed by using this strategy (Scheme 2A). The key step of this transformation was the formation of an alkyl radical via photocatalysis and a dienolate/trienolate intermediate via NHC catalysis. To investigate the mechanism of this alkylation reaction, several control experiments, such as radical trapping and radical clock experiments, were carried out. The plausible mechanism is proposed in Scheme 2B. The alkyl radical 7 is generated via photocatalysis from alkyl halide while the dienolate intermediate 4 is generated from enal 1 via NHC catalysis. The alkyl radical 7 reacts with the dienolate intermediate 4 to afford the homoenolate radical 5, which undergoes single-electron transfer (SET) oxidation with the radical cation of the photocatalyst to give α,β-unsaturated acyl azolium intermediate 6. Lastly, the acyl azolium intermediate 6 is trapped by methanol to afford the corresponding product 3 and liberate the NHC catalyst.

Subsequently, the same group further expanded this strategy to the ring-opening and γ -alkylation of cyclopropane enal (Scheme 2C). This method provided an efficient access to γ -alkylated α,β -unsaturated esters 9. A series of alcohols and brominated compounds 2 reacted smoothly to deliver the target products 9 in 52–95% yields. Unfortunately, other enals, such as epoxy enals and several other cyclopropane enals, failed to couple with brominated compounds. The authors

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C. Present tropic: Dual NHC/photocatalysis



Scheme 1 Overview of NHC-catalyzed transformations.

proposed that the dienolate intermediate could be generated from γ-cyclopropane enal through NHC-catalyzed C-C bond cleavage, which was in agreement with Zhao's pathway. The following similar steps to those in Scheme 2B afforded the product 9 and closed the catalytic cycle.

Apart from the above-mentioned contributions, Ye and coworkers also developed the oxidative Smiles rearrangement reaction via dual NHC/photocatalysis (Scheme 2D).¹⁰ Here, O-aryl salicylaldehydes were transformed into aryl salicylates in the presence of oxygen as the oxidant. This study revealed that the oxidation of the Breslow intermediate was achieved by

A. NHC/photo co-catalyzed γ - and ϵ -alkylation reactions Ru(bpy)₃(PF₆)₂ (2 mol%) Precatalyst **A** (20 mol%) MeOH (5.0 equiv) CsOAc (2.0 equiv) oco₂M€ 32 W CFL, N₂ DCE, 25 °C, 24 h BF NC 3b, 60% B. Plausible mechanism

 ${f C}.$ NHC/photo co-catalyzed ring opening and $\gamma-$ alkylation of cyclopropane enal

D. NHC/photo co-catalyzed oxidative Smiles rearrangement

E. NHC/photo co-catalyzed intramolecular cross dehydrogenative coupling reactions

Scheme 2 NHC/photo co-catalyzed transformations via reaction mode

oxygen with acridinium and NaI as the (co)catalysts and offered a new methodology for oxidative NHC catalysis. Later, this strategy was successfully extended to the intramolecular cross-dehydrogenative coupling of tetrahydroisoquinoline-tethered aldehydes (Scheme 2E).11 Notably, this photoinduced oxidative reaction worked well without an external photocatalyst and an excited Breslow intermediate facilitated the photooxidation course.

Simultaneously, Hopkinson and co-workers developed a novel protocol for the Diels-Alder reaction of acid fluorides with trifluoromethyl ketones via reaction mode b (Scheme 3A).12 In their system, 1,3-dimethylimidazolium triflate C as the precatalyst and Cs2CO3 as the base were Highlight

OT Cs₂CO₃ Photo/NHC Catalytic Cycle 15a 20 1,5-H abstraction

Scheme 3 NHC/photo co-catalyzed Diels-Alder reaction of acid fluorides with trifluoromethyl ketones via reaction mode b.

employed under the irradiation of UVA LEDs. A range of acid fluorides 14 and trifluoromethyl ketones 15 were investigated to verify the wide substrate scope tolerance. Unfortunately, other classes of nonenolizable ketones, such as 2-ketoesters and isatins, didn't work under the current conditions. To gain insight into the reaction mechanism, stoichiometric studies and time-dependent DFT calculations were conducted to support the mechanistic scenario where the combination of the NHC and the acid fluoride led to an interim change in the absorption properties and photochemical reactivity of the carbonyl function. The proposed mechanism is shown in Scheme 3B; the in situ generated NHC reacts with acid fluoride 14a to deliver the o-toluoyl azolium intermediate 17 and releases F-. This azolium intermediate 17 can be excited under UVA irradiation and provides the triplet excited state intermediate 18 after intersystem crossing. Rapid 1,5-H abstraction from the o-benzylic position to the radical-like carbonyl oxygen produces the triplet dienol biradical 19. Rotation of this biradical before relaxation results in the ground state 20, which reacts with the trifluoromethyl ketone 15a in a (4 + 2) cycloaddition process to afford the cycloadduct 21. Finally, elimination of the NHC in the presence of the base gives the desired product 16a and completes the catalytic cycle.

Most recently, another elegant example of combining photocatalysis with NHC catalysis has been demonstrated by Scheidt and co-workers. 13 They developed a novel NHC/photo co-catalyzed alkylation reaction between acyl imidazoles 22 and Hantzsch esters 23 for the efficient synthesis of ketones 24 (Scheme 4A). This method enabled the coupling of an acyl radical with an alkyl radical by using the triazolium salt D as the precatalyst and iridium photocatalyst. To further demonstrate the utility of this method, various pharmaceutical carboxylic acid drugs, such as telmisartan, repaglinide and dehydrocholic acid, were applied for the one-step direct alkylation reaction to afford the corresponding ketone products in moderate to good yields. A series of control reactions and radicaltrapping experiments were performed, which indicated that the oxidation of the Hantzsch ester occurred prior to the reduction of the acyl azolium. The proposed reaction pathway is shown in Scheme 4B. The Hantzsch ester 23a is oxidized to generate the radical cation 25 using the photoexcited catalyst (Ir^{III}*); then cleavage of the radical cation 25 provides the benzyl radical. The following reduction of the acyl triazolium intermediate 26 via IrII gives the crucial azolium radical 27. The final coupling of the benzyl radical and the radical inter-

A. NHC/photo co-catalyzed alkylation reactions Precatalyst **D** (15 mol%) [Ir(dFCF₃ppy)₂(dtbpy)]PF₆ (1 mol%) R2-HE (23) Cs₂CO₃ (15 mol%) **24,** 35-80% yield 467 nm LED, 16 h 24a. 91% 24b. 52%

Scheme 4 NHC/photo co-catalyzed alkylation of acyl imidazoles with Hantzsch esters via reaction mode b.

mediate 28 affords the desired ketone 24c and liberates the NHC catalyst.

In summary, as demonstrated by the examples discussed, dual NHC/photocatalysis will lead to the development of a wide range of novel transformations with broad synthetic applications. This methodology has shown its potential advantage of introducing radicals into NHC catalysis. Although the NHC/photo co-catalyzed reaction is now at the stage of infancy, these studies have impressively illustrated that combining photocatalysis and NHC catalysis is a prospective strategy. In future research, several challenges need to be addressed; a wide range of NHC derived intermediates—especially homoenolate equivalents and α,β -unsaturated acyl azolium intermediates—should be investigated, and compared with well-developed NHC-catalyzed asymmetric reactions, the development of enantioselective approaches is still needed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The School of Chemical Sciences, University of the Chinese Academy of Sciences is gratefully acknowledged.

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